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E-mail: cjim_en@cjim.cn

Evidence-Based Integrative Medicine

Reduning Injection *versus* Neuraminidase Inhibitors in Treatment of Influenza: A Systematic Review and Meta-Analysis*

ZHAO Guo-zhen[1,2,3], LI Bo[2,3,4], WANG Ya-fan[2], GUO Shi-qi[5], DU Yuan[1,2], MA Qiu-xiao[6], GUO Yu-hong[2], and LIU Qing-quan[2,3,4]

ABSTRACT **Objective**: To perform a systematic review to assess the effectiveness and safety of Reduning Injection *versus* neuraminidase inhibitors in treatment of influenza. **Methods**: The MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), Chinese Bio-medical Literature and Retrieval System (Sinomed), China National Knowledge Infrastructure Database (CNKI), China Science and Technology Journal Database (VIP), Wanfang Data Knowledge Service Platform and ClinicalTrails.gov were systematically searched from inception dates to May 2021 for randomized controlled trials (RCTs) exploring Reduning Injection alone or in combination with neuraminidase inhibitors in patients with influenza. Statistical analysis was performed using RevMan 5.4 and Stata 15.1. The qualities of the involved studies were assessed by the risk of bias according to the Cochrane handbook. The evidence quality of each outcome was evaluated by GRADEpro GDT. **Results**: Twelve trials with 1,460 patients were included. The included studies had a certain unclear or high risk of bias. Reduning Injection appeared to be more effective in shortening the fever clearance time (MD: –16.20 h, 95% CI: –19.40 to –12.99, 7 trials, 814 patients, I^2=94%, very low certainty), fever alleviation time (MD: –4.09 h, 95% CI: –4.22 to –3.96, 3 trials, 366 patients, I^2=0%, low certainty), cough alleviation time (MD: –21.34 h, 95% CI: –41.56 to –1.11, 2 trials, 228 patients, I^2=89%, very low certainty), fatigue alleviation time (MD: –31.83 h, 95% CI: -36.88 to –26.77, 2 trials, 270 patients, I^2=0%, low certainty), sore throat alleviation time (MD: –28.66 h, 95% CI: –32.23 to -25.10, 1 trial, 150 patients, low certainty), and improving the total effective rate (RR: 1.15, 95% CI: 1.06 to 1.25, 10 trials, 1,074 patients, I^2=76%, very low certainty). Besides, Reduning Injection seemed generally safe. **Conclusions**: This study provided low or very low evidence indicating Reduning Injection may be effective in the treatment of influenza and might be safe. Further rigorously designed studies are needed to confirm the effectiveness and safety of Reduning Injection and support it as a recommendation for influenza.

KEYWORDS Chinese patent medicine, Reduning Injection, influenza, meta-analysis, systematic review

Influenza is an acute respiratory infectious disease which is caused by influenza virus,[1] and is manifested with fever, cough, sore throat, headache, fatigue, etc. Due to the high mutation rate of influenza virus, people are generally susceptible to the infection,[2] and influenza has become the most common infectious disease worldwide.[3] It is estimated that about 5%–10% of adults and 20%–30% of children may suffer from seasonal influenza each year,[1] causing 291,243–645,832 deaths and seriously endangering people's health.[4] Neuraminidase inhibitors (NALs) such as oseltamivir, peramivir and zanamivir are mainly recommended therapies in the guidelines for suspected or confirmed cases of influenza.[5-7] However, NALs have limitations: oseltamivir takes effect only when it is taken within 48 h

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1. School of Clinical Medicine, Beijing University of Chinese Medicine, Beijing (100029), China; 2. Department of Emergency, Beijing Hospital of Traditional Chinese Medicine, Capital Medical University, Beijing (100010), China; 3. Beijing Evidence-Based Chinese Medicine Center, Beijing (100010), China; 4. Beijing Institute of Chinese Medicine, Beijing (100010), China; 5. School of Acupuncture-Moxibustion and Tuina, Beijing University of Chinese Medicine, Beijing (100029), China; 6. Department of Respiratory, Xiyuan Hospital, China Academy of Chinese Medical Sciences, Beijing (100700), China
Correspondence to: Prof. LIU Qing-quan, E-mail: liuqingquan2003@126.com

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after the onset of symptoms;[8] the severity of symptoms and influenza virus strains affected the effect of NALs;[9] and extensive use of NALs may increase the risk of drug resistance.[10] Because of these, more alternative therapies have been considered.

In China, Chinese medicine (CM) has played an important role in the treatment of influenza. In clinical practice guideline (CPG) on treating influenza in adult patients with Chinese patent medicines (CPMs),[11] 5 CPMs have been recommended to be used alone in mild influenza patients, not necessarily in combination with Western medicine. However, the recommendations of this CPG were all oral CPMs, and there was no recommendation for CPM injections.

Reduning Injection (热毒宁注射液, RDN) is extracted from 3 Chinese herbs including *Artemisia annua* L, *Lonicera japonica* T. and *Gardenia jasminoides* E. It has been reported that the components of RDN have potential antiviral, anti-inflammatory and immunomodulatory functions,[12-14] and is often clinically used to treat influenza patients with external contraction of wind-heat syndrome or heat-toxin attacking the Lung (Fei) syndrome. Previously published clinical trials have proved the effect of RDN on treating influenza, such as shortening the clearance time of fever and alleviation time of influenza symptoms.[15,16] However, there has been no critical evaluation of current evidence from RCTs for RDN in treatment of influenza. Therefore, we performed a systematic review and meta-analysis to clarify the effectiveness and safety of RDN use alone or in combination with NALs.

METHODS

The review protocol was registered in PROSPERO platform (No. CRD42021228626, available at: https://www.crd.york.ac.uk/PROSPERO/). We followed the reporting standard for systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement checklist.[17]

Data Sources and Search Strategy

We identified all relevant articles in accordance with the Cochrane Handbook.[18] and originally searched publications in the following electronic databases from inception dates to May 1st, 2021 including MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), Chinese Bio-medical Literature and Retrieval System (Sinomed), China National Knowledge Infrastructure Database (CNKI), China Science and Technology Journal Database (VIP) and WanFang Data Knowledge Service Platform. We also searched ClinicalTrails.gov for relevant ongoing or unpublished trials. The following search terms were used: "influenza", "human flu" and "Reduning Injection", etc. The search strategy of MEDLINE as an example is presented in Appendix 1. The references of the included articles were searched to find any additional articles.

Criteria of Inclusion

Types of Study Design

Randomized controlled trials (RCTs), regardless of the usage of blinding, language, and publication type, were included. Studies were excluded in the case of duplicate studies, non-RCT, no definite diagnosis of influenza and unable to obtain full-text.

Types of Participants

To be included in the review, patients should be diagnosed as influenza, irrespective of the patient's gender and age. The diagnostic criteria of influenza included feeling unwell within 36 h, having fever (≥38 ℃ if age <65 years; ≥37.5 ℃ if age ≥65 years), and at least two influenza symptoms (one respiratory symptom: cough, sore throat or coryza; and general symptom: headache, myalgia, sweats or chills, or fatigue).

Types of Intervention

The interventions were RDN, at any dose or with any duration, used alone or in combination with NALs (oseltamivir, peramivir and zanamivir), without restriction on dosage or treatment duration.

Types of Control

The interventions used in control group were NALs therapies.

Types of Outcomes

The primary outcomes were fever clearance time. The secondary outcomes included the fever alleviation time, other symptoms alleviation time, total effective rate, and adverse events (AEs). The fever clearance time was defined as time from baseline to the first time when axillary temperature decreased to <37.4 ℃ and maintenance of stable temperature (<37.4 ℃) more than 24 h, and the fever alleviation time was defined as time from baseline to the first time when

axillary temperature descended more than 0.5 ℃. Considering that there are 7 common symptoms of influenza: nasal congestion, sore throat, cough, aches and pains, fatigue, headaches, and chills or sweats,[19] we conducted meta-analysis for each symptom reported in the included studies for the outcome of symptoms alleviation time. Effective was defined as a decrease in body temperature and symptom relief.

Study Selection

Two authors (Zhao GZ and Ma QX) independently screened titles/abstracts and read the full text of potential studies in duplicate to identify articles that met the inclusion criteria. The authors resolved any disagreements through discussion, and if disagreements were not resolved, a third author (Li B) was invited to arbitrate.

Data Extraction

A pre-defined form was designed and used to extract information from the selected studies, including study characteristics (e.g., author name, published year, sample size), patients' information (e.g., gender, age), interventions and control characteristics (e.g., specific medication, dose, duration), and outcomes (primary and secondary outcomes specifically mentioned above). Data extractions were performed by two independent authors (Wang YF and Guo SQ). Any disagreements were resolved by discussion or asked a third author (Guo YH) to arbitrate.

Quality Assessment

Authors (Zhao GZ and Du Y) independently assessed risks of bias of included RCTs using the Cochrane Collaboration risk of bias tool by RevMan 5.4.[18,20] The 7 domains were assessed including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias. Each domain was judged as "low", "high", or "unclear" risk of bias.

Data Synthesis and Analysis

Stata (version 15.1) was used for data analysis. Risk ratios (RR) with 95% confidence interval (CI) was calculated for dichotomous variables. For continuous variables, the weighted mean difference (WMD) with 95% CI was used if the measurement method and unit were the same, otherwise the standard mean difference (SMD) with 95% CI was used. Intention-to-treat (ITT) analysis was conducted. The Cochran's Chi-square test and I^2 statistic was used to evaluate heterogeneity. If statistical heterogeneity was present (P<0.10, or I^2>50%), the random-effects model was used, otherwise the fixed-effect model was adopted.[21] For the primary outcomes, consideration that the included studies had differences in study population and intervention, random-effects model as the primary analysis and fixed-effect model as the sensitive analyses were used. The funnel plot, begg's text and egger text were used to assess the publication bias if more than 10 RCTs were included for each outcome.

Assessment of Evidence Quality

Grading of Recommendations Assessment, Development and Evaluation (GRADE) system approach was used to rate the certainty of evidence for each outcome. According to the GRADE guideline,[22-27] the initial certainty of evidence body begins with high on RCTs, and may be decreased if they meet the downgrade criteria (risk of bias, inconsistency, indirectness, imprecision, and publication bias). The certainty of evidence was rated as high, moderate, low, and very low. The summary of findings table was created by the GRADEpro GDT (https://gradepro.org/).

RESULTS

Description of Studies

The search processes are shown in Figure 1 according to PRISMA flowchart. A total of 485 articles was initially identified, and 345 were potentially eligible after removal of duplications. According to inclusion criteria, 290 references were removed by screening title and abstract, and additional 43 studies were excluded after reading full-texts. Finally, 12 studies[15,16,28-37] met the eligibility criteria and were included.

The characteristics of the included studies are summarized in Table 1. One trial[16] was published in English and the rest were in Chinese. A total of 1,460 patients with influenza were included, 734 in the RDN group and 726 in the control group. The sample size of included trials ranged from 38 to 236. The duration of treatments ranged from 3 to 7 days, with an average of 4.33 days. The participants of 5 studies[28-30,32,34] were children, while the others were adults. Five included studies reported CM symptom, and 4[15,33,34,36] of them were heat-toxin attacking Fei and 1[35] was external contraction of wind-heat

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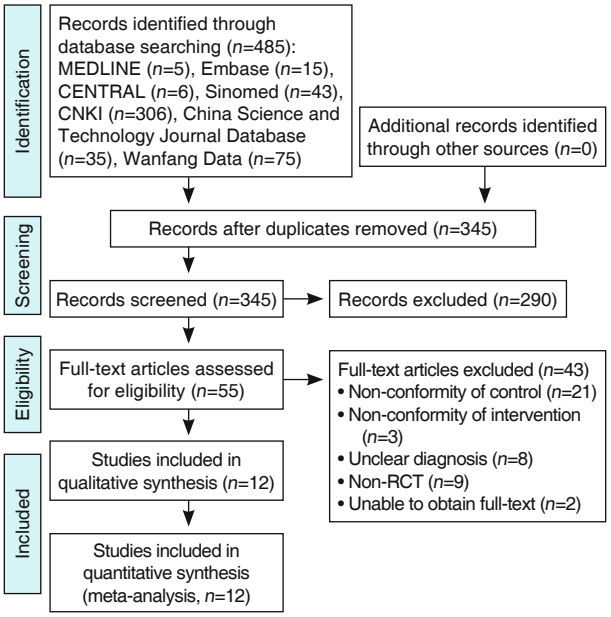

Figure 1. Flow Diagram of Study Selection

symptom. One RCT[36] explored the effects of RDN used alone, 3 RCTs[15,16,33] used RDN plus oseltamivir placebo, while the others used RDN plus oseltamivir. For control group, all articles used oseltamivir alone or in combination with RDN placebo.

Quality Assessment

The methodological quality of included RCTs is summarized in Figure 2. Six trials[16,30,33-35,37] specified the method on sequence generation of randomization which were assessed as low risk. Because of central randomization design, 2 trials[16,33] were evaluated as low risk on allocation concealment. For blinding assessment, considering the use of placebo and choice of objective outcomes, 8 trials[15,16,29,33-35,37,39] were assessed as low risk. All studies had low attrition bias because all participants were accounted. As protocol or registration information of trials were unavailable, 11 RCTs[15,28-37] were assessed as unclear on reporting bias. Another one RCT is available for registration information and has no risk of bias, then it is rated as low. Two trials[15,16] which sponsored by pharmaceutical companies were assessed as high risk, 2 trials[35,36] with sponsorship of government were assessed as low risk, and the other studies were as unclear risk.

Outcomes Evaluation

Fever Clearance Time

Seven studies[15,29,30,33-35,37] involving 814 patients

Table 1. Study Characteristics

Study ID	Sample size	Age range/ mean age (years)	CM symptom	Treatment group (dose of RDN)	Control group	Duration (d)	Outcomes
An 2019[28]	N=180 T/C=90/90	T: 2–11/7.13 ± 3.11 C: 2–10/7.78 ± 3.12	NR	RDN (10 mL) + oseltamivir	Oseltamivir	5	D, E
Gu 2016[15]	N=220 T/C=108/112	18–65 / NR	Heat-toxin attacking Fei syndrome	RDN (20 mL) + oseltamivir placebo	Oseltamivir + RDN placebo	3	A, B, C, E
Hu 2011[29]	N=78 T/C=40/38	T: 0.5–8/3.98 ± 2.39 C: 0.5–7/4.12 ± 3.42	NR	RDN (0.5 mL/kg) + oseltamivir	Oseltamivir	7	A, B, D, E
Hua 2020[30]	N=120 T/C=65/55	T: 3–14/5.9 ± 2.3 C: 0.5–13/5.9 ± 2.6	NR	RDN (change with age) + oseltamivir	Oseltamivir	7	A, D, E
Ji 2011[31]	N=120 T/C=60/60	T: 12–39/22.3 C: 12–39/22.9	NR	RDN (20 mL) + oseltamivir	Oseltamivir	3	D, E
Liu 2017[16]	N=236 T/C=118/118	NR/37.43	NR	RDN (20 mL) + oseltamivir placebo	Oseltamivir + RDN placebo	5	A, C, E
Lv 2019[32]	N=58 T/C=29/29	1–5/2.93 ± 1.78	NR	RDN (0.5 mL/kg) + oseltamivir	Oseltamivir	5	D, E
Sun 2013[33]	N=38 T/C=19/19	T: NR/28.4 C: NR/27.6	Heat-toxin attacking Fei symptom	RDN (20 mL) + oseltamivir placebo	Oseltamivir + RDN placebo	3	A, C, D, E
Xiao 2020[34]	N=150 T/C=75/75	T: 3–14/7.22 ± 0.97 C: 3–14/7.05 ± 1.02	Heat-toxin attacking Fei symptom	RDN (0.3–0.5 mL/kg) + oseltamivir	Oseltamivir	5	A, B, E
Ye 2017[35]	N=100 T/C=50/50	T:18–44/27.02 ± 7.09 C:18–45/28.14 ± 7.11	External contraction of wind-heat symptom	RDN (20 mL) + oseltamivir	Oseltamivir + RDN placebo	3	A, D, E
Zhang 2012[36]	N=52 T/C=26/26	T: 25–58/42.12 C: 30–62/39.84	Heat-toxin attacking Fei symptom	RDN (20 mL)	Oseltamivir	3	D, E
Zhao 2019[37]	N=108 T/C=54/54	T: 20–51/35.5 ± 4.4 C: 21–47/34 ± 3.6	NR	RDN (20 mL) + oseltamivir	Oseltamivir + RDN placebo	3	A, C, D, E

Notes: T: treatment group; C: control group; RDN: Reduning Injection; A: fever clearance time; B: symptoms alleviation time; C: fever alleviation time; D: total effective rate; E: adverse events; NR: not reported

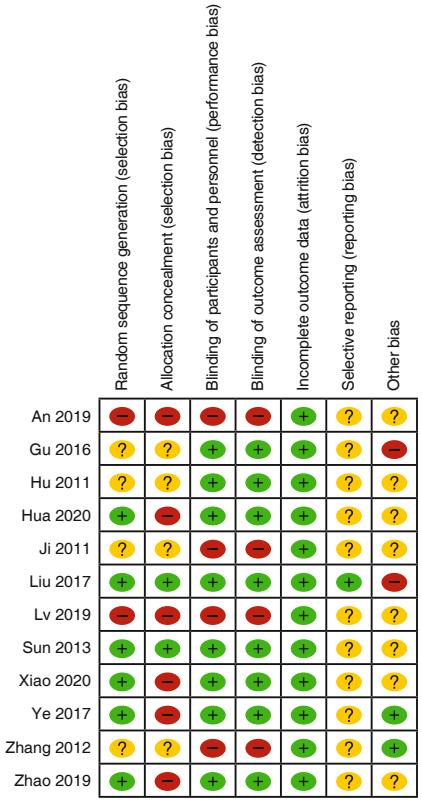

Figure 2. Risk of Bias Summary

reported the outcome of fever clearance time. Given the differences in population and dosage, random-effects model was used for primary analysis and fixed-effect model for sensitive analyses. The meta-analysis showed that compared with the control group, the fever clearance time was significantly shorter in RDN group (MD: –16.20 h, 95% CI: –19.40 to –12.99, I^2=94%, P<0.00001), and fixed-effect model showed a larger effect size (MD: –16.38 h, 95% CI: –16.85 to –15.91, I^2=93.5%, P=0.000; Figures 3A and 3B).

Alleviation Time for Fever

Three studies[15,33,37] including 366 patients reported the outcome of fever alleviation time. The total meta-analysis showed favorable effects of RDN group with no statistical heterogeneity (MD: –4.09 h, 95% CI: –4.22 to –3.96, I^2=0%, P=0.74; Figure 3C).

Alleviation Time for Influenza Symptoms

Among the common symptoms of influenza, there are 3 were mentioned in included studies, which are cough, fatigue, and sore throat. We conducted meta-analyses on the alleviation time of these 3 symptoms.

Alleviation Time for Cough

Two studies[29,34] of 228 patients reported

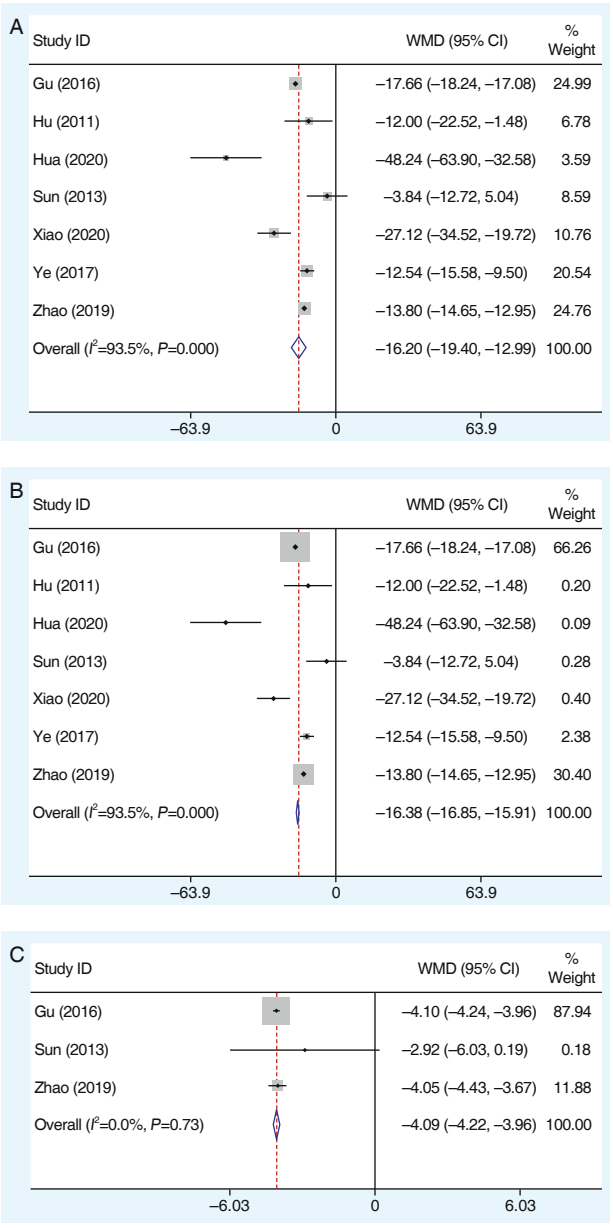

Figure 3. Forest Plot of Comparison for Fever Clearance (A and B) and Alleviation Time (C)
Notes: A: Random-effects model; B: Fixed-effects model

the outcome of cough alleviation time. There was significant heterogeneity in this analysis, so the random-effects model was used. The meta-analysis showed that RDN group significantly decreased the cough alleviation time when compared to control group (MD: –21.34 h, 95% CI: –41.56 to –1.11, I^2=89%, P=0.003; Figure 4A).

Alleviation Time for Fatigue

Two studies[30,34] of 270 patients reported the outcome of fatigue alleviation time. The meta-analysis result showed a favorable effect of RDN on shortening

the fatigue alleviation time (MD: -31.83 h, 95% CI: –36.88 to –26.77, I^2=0%, P=0.42; Figure 4B).

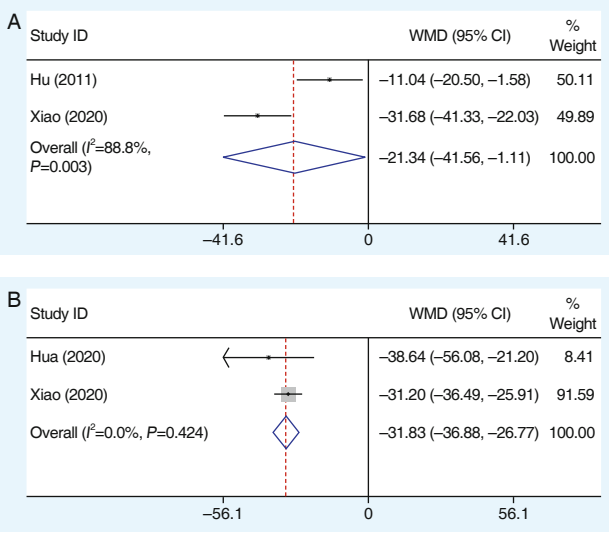

Figure 4. Forest Plot of Comparison for Symptoms Alleviation Time

Notes: Forest plot of cough (A) and fatigue (B) alleviation time

Alleviation Time for Sore Throat

Only one study[34] reported the outcome of sore throat alleviation time. The result showed that compared with the control group, the sore throat alleviation time was significantly shorter in the treatment group (MD: –28.66 h, 95% CI: –32.23 to –25.10).

Total Effective Rate

Ten studies[15,28-33,35-37] involving 1,074 patients reported the outcome of total effective rate. The random-effects model was used because of the significant heterogeneity. The meta-analysis showed a significant higher effective rate in the RDN group compared with the control group (RR: 1.15, 95% CI: 1.06 to 1.25, I^2=76%, P<0.0001; Figure 5).

Frequency of AEs

Seven out of the 12 studies reported AEs, of which 3 studies[31,33,36] indicated that there were no obvious AEs. Four studies[15,16,28,30] reported AEs such as transfusion reaction, descended leukopenia, and increased lymphocytes, etc. A meta-analysis of these 4 studies involving 756 patients reported case numbers of AEs, and showed no significant differences between two groups (RR: 0.90, 95% CI: 0.30 to 2.68, I^2=70%, P=0.02; Figure 6).

Publication Bias

As we only included more than 10 trials with

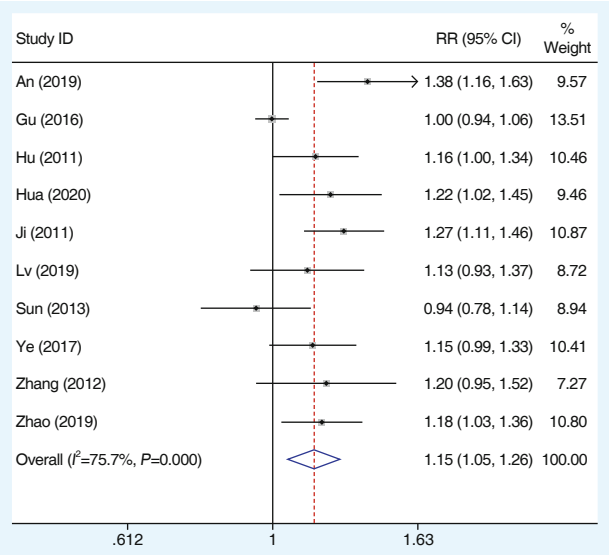

Figure 5. Forest Plot of Comparison for Total Effective Rate

Note: Weights are from random effects analysis

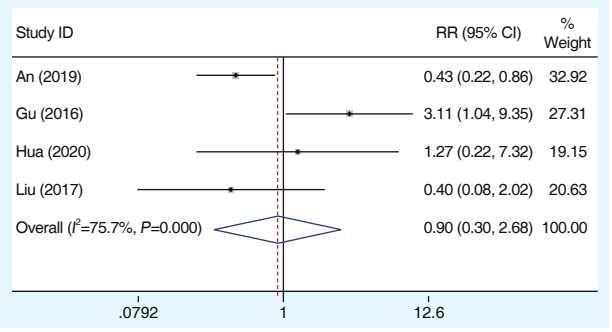

Figure 6. Forest Plot of Comparison for Frequency of Adverse Events

Note: Weights are from random effects analysis

usable data in the meta-analysis of total effective rate, we constructed a funnel plot, begg's test and egger test on this outcome (Figure 7). The begg's test and egger test of total effective rate demonstrated no significant symmetry (Begg's test, P=1.409; Egger test, P=0.193).

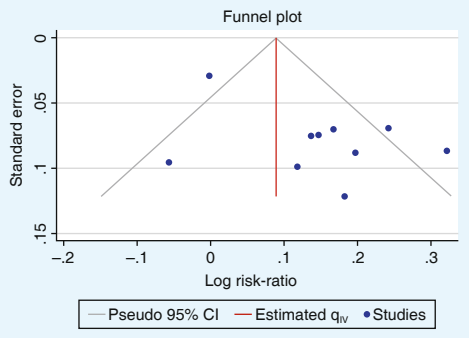

Figure 7. Funnel Plot of Publication Bias for Total Effective Rate

Summary of Findings Table

The overall evidence on 7 outcomes were evaluated by GRADE (Appendix 2). Generally, the evidence quality was low for alleviation time of fever, fatigue, and sore throat, and very low for fever clearance time, cough alleviation time, total effective rate, and AEs.

DISCUSSION

This study included 12 RCTs and systematically evaluated the effectiveness and safety of RDN for influenza. The results showed that compared with NALs, the RDN use alone or in combination with NALs could shorten the fever clearance time by 16.20 (19.40—12.99) h, which has certain clinical significance. In addition, RDN showed better effects on fever and symptoms alleviation time as well as total effective rate. Besides, RDN seemed generally safe.

For influenza patients, fever, cough, sore throat, fatigue, and other symptoms caused by influenza virus are the most important factors affecting the quality of life of patients, and fever is the most important factor. Therefore, the strength of this systematic review is that we used the remission time of influenza-related symptoms as outcomes to evaluate the efficacy of RDN.

Relevant studies showed that RDN may have potential advantages on other diseases.[38] As the development of a new antiviral drug is generally slow,[39] it may not be timely to provide a suitable antiviral drug in face of a new and acute respiratory viral infection, such as coronavirus disease 2019 pandemic.[40] Considering the mechanism of RDN, it may have effects on acute respiratory infectious diseases caused by other viruses. However, the conclusion needs to be confirmed by relevant clinical studies.

We speculate that the significant effects of RDN in treating influenza may be explained by the following reasons. Firstly, RDN could alleviate lung damage and improve survival by reducing the viral titers in lungs, and reducing key inflammation-regulating factors including interleukin (IL) -1β, IL-6, IL-10 and IL-18.[41,42] Secondly, the components of RDN, including *Artemisia annua* L, *Lonicera japonica* T. and *Gardenia jasminoides* E, have been proven to have potential antiviral function, as well as significant anti-inflammatory and immunomodulatory function.[43,44]

Relevant studies showed that there was no significant difference in changes of viral titer when compared CM with NALs in the treatment of influenza.[45] However, this study found that RDN can shorten the onset of some flu symptoms, such as fever, cough, sore throat, and fatigue. Therefore, clinicians can use RDN with reference to the results of this study for flu patients with severe symptoms.

According to CPG on treating influenza in adult patients with CPM,[11] influenza patients can be divided into mild, severe, and critical cases, and staged treatment may be performed. However, few studies clearly indicated the stage of influenza, making it difficult to judge the severity of disease and provide treatment recommendations. Further studies should be carried out on influenza patients with different severity, to further evaluate the effectiveness and safety of RDN on different stages of influenza.

There are some limitations in this study. Firstly, the combined results of some outcomes were statistically heterogeneous, but we cannot perform subgroup analysis or sensitive analysis due to insufficient number of original studies, the random-effects model was chosed for meta-analysis. Secondly, most of the included studies had flaws in methodological design, such as unclear allocation concealment or lack of clinical trial registration, so whether there was a selection bias or reporting bias was unclear. Thirdly, all included RCTs were from China, which may limit the application of the results.

Due to the heterogeneity and bias risk of the included trials, the certainty level of evidence was downgraded. Therefore, it is necessary to carry out large sample, high-quality, multi-center clinical trials. In order to reduce the risk of bias and improve the evidence level, it is necessary to register the research protocol, use computer-generated random sequences, conceal the allocation scheme, and imply blind for participants and outcome evaluators. Among them, blinding of patient can be achieved through using saline as RDN simulation, using brown infusion tube in infusion operation, and so on. Additionally, more rigorous researches are needed to evaluate the safety of RDN, such as phase Ⅳ clinical trials.

This meta-analysis provided low or very low evidence indicating RDN may have effects in treatment of influenza on shortening the clearance time of fever, the alleviation time of fever, cough, fatigue, and sore throat, as well as increasing the total effective rate, and might be safe. More large-scale, high-quality, multicenter clinical trials with appropriate outcome indicators are needed to prove the effectiveness and safety of RDN.

Availability of Data and Materials

The datasets analyzed in this study are supported by the published articles in opening electronic databases (details in search strategy).

Conflict of Interest

All authors have completed the International Committee of Medical Journal Editors (ICMJE) uniform disclosure form. The authors have no conflicts of interest to declare.

Author Contributions

Conception and design: Zhao GZ, Li B and Liu QQ; administrative support: Guo YH and Liu QQ; Provision of study materials or patients: Zhao GZ and Ma QX; collection and assembly of data: Wang YF and Guo SQ; data analysis and interpretation: Zhao GZ and Du Y; Manuscript writing: Zhao GZ; final approval of manuscript: All authors.

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